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Alzheimer's & Dementia

Featured Article

Protective effect of antirheumatic drugs on dementia in rheumatoid arthritis patients

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Abstract

Introduction: Rheumatoid arthritis is a systemic inflammatory disease, and classical disease-modifying antirheumatic drugs (cDMARDs) have proven efficacy. It is unknown what impact cDMARDs might have on dementia as an outcome.

Methods: Incident diagnoses of rheumatoid arthritis in persons over 18 years from 1995 to 2011 were identified from the UK Clinical Practice Research Datalink. There were 3876 cDMARD users and were propensity score matched to 1938 nonusers, on a wide range of confounders. Impact on dementia was assessed using survival models.

Results: cDMARD users were at reduced risk of dementia (hazard ratio: 0.60; 95% confidence interval: 0.42–0.85). The effect was strongest in methotrexate users (hazard ratio: 0.52; 95% confidence interval; 0.34–0.82).

Discussion: The strong effect of cDMARD use on halving of dementia risk requires replication in a trial and may provide an important therapeutic pharmacological treatment.

Keywords: Dementia; Rheumatoid arthritis; Epidemiology; Disease-modifying antirheumatic drugs (DMARDs); Methotrexate; Propensity score matching; Fine and gray models; Clinical Practice Research Datalink; Alzheimer's disease

1. Introduction

There are 850,000 people in the UK living with dementia in 2015, with an estimated cost of £26.3 billion per year [1]. Although pharmacological interventions are now recommended by guidelines for managing the cognitive symptoms of mild-to-moderate Alzheimer's disease (AD), importantly, for other types of dementia such as vascular dementia, these drugs are not recommended [2].

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Rheumatoid arthritis (RA) is a chronic autoimmune disease causing pain and inflammation in the joints [3], ultimately leading to joint destruction and deformity. RA affects between 0.5% and 1% of the general population [4]. The economic impact is substantial with the total cost of disease in the UK estimated to be between £3.8 and £4.8 billion per year [2]. Classical disease-modifying antirheumatic drugs (cDMARDs) have proven efficacy and can control disease activity, reduce joint erosions [5], and improve quality of life [6]. Current guidance recommends a combination of cDMARDs (including methotrexate [MTX] and at least one other cDMARD, plus short-term glucocorticoids) as first line treatment, ideally within 3 months of symptom onset for people with recently diagnosed active RA [2].

RA has been used as a model of negative consequences of systemic inflammation such as cardiovascular disease, and the cDMARD MTX is effective at reducing this [7]. In addition, other systemic inflammatory events not involving the central nervous system are associated with an increased production of the peripheral cytokine tumor necrosis factor-α, increasing the risk of decline in AD [8].

For this reason, it seems reasonable to suggest that cDMARDs, such as MTX, may prove beneficial for the treatment of dementia where an inflammatory insult is caused, such as protective effects have previously been observed in patients exposed to arthritis or antiinflammatory drugs [9].

The aim of this study is to describe the association of cDMARD use on dementia development using data on a large cohort of patients with incident RA from the UK Clinical Practice Research Datalink (CPRD).

2. Methods

2.1. Study design, setting, and source of data

We conducted a population-based retrospective cohort study. Data were obtained from the UK CPRD [10]. The CPRD comprises the entire computerized medical records of a sample of patients attending general practitioners in the UK, covering a population of 6.5 million patients from 433 contributing practices chosen to be representative of the wider UK population. General practitioners in the UK play a key role in the delivery of health care by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The CPRD is administered by the Medicines and Healthcare products Regulatory Agency of UK.

The CPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, and hospital admissions. Data are stored using "Read Codes" for diseases that are cross-referenced to the International Classification of Diseases. Read Codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the CPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the CPRD.

2.2. Participants

For the study population, the database was screened to identify a first-ever clinical or referral record of RA occurring from 1995 until the end of 2011, identified in CPRD using a Read code, and occurring within the patients up-to-standard registration period (Supplementary Table 1). Patients had to have at least 1 year's up-to-standard registration in CPRD before the index date. The validity of an RA diagnosis in CPRD is high [11] for patients with specific characteristics when using the American College of Rheumatology diagnostic criteria as the standard [12]. To ensure the validity of the RA diagnosis, we used the same Read codes in the diagnostic groups used in the previous RA validation study [11], and patients were only included if they had more than one medical code for RA on different dates. The study population only included incident patients (those with a first-ever record of RA at least 1 year after start of data collection) who were aged 18 years or older at the date of diagnosis. Using these criteria, we identified 11,772 patients eligible for the present study.

2.3. Outcome and exposure

The outcome was incident dementia using standard UK clinical terminology Read Codes (Supplementary Table 2). This definition included AD, vascular dementia, and mixed dementia. Patients were followed up to 15 years from the date of RA diagnosis. The exposure was whether or not a patient had been prescribed a cDMARD after RA diagnosis. cDMARDs selected for this study based on their frequency within the data set were as follows: MTX, MTX sodium, chloroquine phosphate/proguanil hydrochloride, ciclosporin, cyclophosphamide, hydroxychloroquine sulphate, sodium aurothiomalate, and sulfasalazine. For the purposes of analysis, patients were categorized according to whether or not they had been prescribed any cDMARD. As MTX is among the most effective cDMARDs for patients with RA with less toxicity and better tolerability, we further categorized cDMARD use according to whether or not a patient was prescribed MTX.

2.4. Potential confounders

Confounding variables included age, sex, body mass index (closest height, weight, and body mass index measurements to the date of diagnosis), alcohol consumption, smoking, calendar year of RA diagnosis, duration of RA (time since first-ever record of RA), region of the UK, comorbidities (tuberculosis, demyelinating disease, cardiovascular disease, myocardial infarction, congestive

heart failure, peripheral vascular disease, interstitial lung disease, anemia, and osteoporosis), first presenting symptoms for early RA (joint pain, swollen tender joints, morning stiffness, systemic malaise, weakness/loss of energy), medication use in the year before RA diagnosis (analgesics, hypertensives, aspirin, cyclooxygenase-2 inhibitors, diabetic medications, H2 blockers, nonsteroidal antiinflammatory drugs [NSAIDS], proton pump inhibitors, statins, prednisolone, and other steroids), steroid use after RA diagnosis (prednisolone and other steroids), whether or not the patient has severe RA (systemic disease [extra-articular], seropositivity, erosive, multiple joint, or polyarthropathy) at the time of diagnosis.

2.5. Statistical methods

In randomized controlled trials, each person has an equal probability of being in a treatment or control group. Observational study designs are limited by an inherent imbalance of both known and unknown confounders making some patients more likely to receive cDMARDs than others. As receipt of cDMARD was not randomly allocated in our study, confounding by indication was accounted for by using propensity score matching methods. Use of these methods for the assessment of causality in epidemiological studies has been previously described [13].

The propensity score represents the probability that a patient received the intervention (cDMARDs). In an RCT, the propensity score is 50%, as each person has equal probability of being in the treatment or control group. With a propensity score, treated and control patients are matched according to their probability of receiving treatment. For example, a treated patient with a 75% chance of receiving treatment is compared with a control with a 75% chance of receiving treatment, and so on, across the full distribution of probabilities.

To create a propensity score, a logistic regression model is fitted where the outcome is cDMARD user (yes/no); and the covariates listed previously are all included as potential confounders. Based on the variables included in the model, the propensity score is the predicted probability of a person receiving outcome (cDMARD user or nonuser).

Having created a propensity score, and to address the issue of confounding by indication, matching is used. Patients with contraindications to use of a drug may have no comparable exposed subjects. A matched analysis will exclude those cDMARD users with no comparable nonuser controls [14]. Propensity scores are used to match each patient not receiving cDMARDs to two comparable cDMARD users. Greedy matching is used, where a random treated subject is selected and a nearest neighbor (untreated subject) then selected for matching. Matched treated and untreated subjects can only have propensity scores that differ by at most a fixed, prespecified amount (the caliper width). We chose a 0.02–standard deviation caliper width [15].

Immortal time bias is a common issue in epidemiological studies, where the event of interest cannot occur for a certain time span [16]. In the case of this proposed study, immortal time bias would occur because of the definition of exposure, where in the time from diagnosis of incident RA till receipt of cDMARDs those in the "cDMARD user group" cannot have the outcome by design, otherwise they would have been classified as nonusers. To avoid the problem of immortal time bias, we use time-varying exposures, where in a survival analysis, the time period previous to the index date of cDMARD treatment initiation (i.e., first prescription of a cDMARD) is reclassified as nonuser for those in the cDMARD user group.

Matched cDMARD users and their non-cDMARD user controls were included in survival regression models to describe the association between cDMARD use and time to outcome. Consideration of competing risks is required, where death is an important competing risk that precludes development of dementia. A standard Cox regression survival model treats the competing risk of death as a censored observation, but this assumes death is noninformative (e.g., that if they had not died, they would have the same chance of developing dementia as their peers). To account for the competing risk of death, we used the method of "Fine and Gray". This allows us to model the risk of dementia in those who are currently event free and those who have previously experienced a competing event (rather than only include those in the risk set that have not died).

As we have a matched sample, this introduces a bias that must be accounted for in the analysis stage. Matched subjects will have correlation (greater similarity) in outcomes than two randomly selected subjects. This is because their baseline covariates are more similar, and baseline covariates are related to outcomes.

We must therefore account for the lack of independence in outcomes that have been induced by matching.

Hence, to account for the matched nature of the sample, we use a robust variance estimator that accounts for the clustering within matched sets [17]. The proportional hazards assumption was assessed using Schoenfeld's residuals, that is, it was tested that the survival probability in exposed and nonexposed patients was proportional over time. Kaplan-Meier plots were used to estimate the probability of dementia up to 15 years following RA diagnosis in matched cDMARD users and nonusers.

Stata, version 13.1 (Stata, College Station, TX, USA), was used for all statistical analyses.

3. Results

Data were available for 11,772 patients with incident RA, of whom 8312 (70.6%) became cDMARD users. They were followed for a median (interquartile range) of 6.5 (3.4–9.9) years (cDMARD users) and 5.1 (2.2–8.6) years (nonusers). At the time of RA diagnosis, those who went on to become cDMARD users were younger (mean age 58.3 years)

compared with nonusers (mean age 65.9 years), and a similar proportion of patients were female (~70%) in both exposure groups (Supplementary Table 1). cDMARD users were more likely to drink and smoke, but less likely to have comorbidities (particularly cardiovascular related comorbidities) and less likely to be taking medications (e.g., antihypertensive) and steroids (prednisolone) before RA diagnosis. Over the study period, the percentage of patients receiving cDMARDs increased over time—in 1995, only 63.5% of patients were cDMARD users, and this had increased to over 80% of patients by 2009.

Propensity-score logistic regression models achieved a C-statistic (corresponding to the area under the receiver operating characteristic curve) of 0.71 for cDMARD users versus nonusers, indicating moderate imbalance with respect to the wide range of measured confounding factors before propensity score matching was applied. Fig. 1 demonstrates how the cDMARD user and nonuser groups have become balanced on known and measured confounders after propensity score matching—particularly in respect of age, comorbidities, and medication use. In the matched population, there were 3876 cDMARD users and 1938 nonusers, and only these patients are included in all subsequent analyses. Of the cDMARD users, 2355 (60.8%) received MTX, and 1521 (39.2%) received other cDMARDs.

Dementia outcome was uncommon with 15-year rates of 2.0%. We observed a reduced risk of dementia in cDMARD users versus nonusers, these being 0.5% versus 1.6% at 5 years and 1.5% versus 3.0% at 15 years. There was a strong reduction in the risk of dementia for cDMARD users (hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.42–0.85), with the effect being strongest in MTX users (HR: 0.52; 95% CI: 0.34–0.82) versus non-MTX users (HR: 0.70; 95% CI: 0.32–1.08).

Kaplan-Meier plots provide a visual assessment of the effect of cDMARD use on dementia incidence (Fig. 2) over the duration of the 15-year follow-up. For dementia, a significant difference is first observed at around 3 years of follow-up, with lower risk of dementia in cDMARD users with this difference remaining significant at over 10 years of follow-up.

4. Discussion

4.1. Main findings

Although dementia was uncommon, the large sample size afforded by the study allowed us to identify a highly significant reduction in risk of dementia in cDMARD users versus nonusers, these being 0.5% versus 1.6% at 5 years and 1.5% versus 3.0% at 15 years. These percentages are concordant with an estimated prevalence of 1.3% for the entire UK population in 2013 [1], bearing in mind that incidence is being deferred to older ages. The observed associations of cDMARD use with reduced dementia risk suggest this may be a potential therapeutic option for patients with dementia, for whom no pharmacological drug treatments are available or recommended, and would require further exploration in future randomized controlled trials.

4.2. What is already known

RA is an inflammatory disease that can also cause inflammation in other parts of the body, including the heart, lungs, and blood vessels [18]. In turn, dementia has biomarker changes indicative of inflammatory insult [19]. Inflammation is a common characteristic of both RA and dementia, and this fact is supported by common inflammatory biomarkers that are being found in both diseases (e.g., interleukin-6 [20,21], interleukin-12 [22,23], C-reactive protein [20,24], pentraxin 3 [25,26], endothelin-1 [27,28], resistin [25,29], and receptors for advanced glycation end products [25,30]). There is also an association between the levels of cytokines important in the pathogenesis of RA, such as tumor necrosis factor-α or interleukin-10, and progression of dementia [8,31,32]. The widespread reporting of reductions in cardiovascular events associated with MTX use, many initially seen in patients with RA, has subsequently led to large-scale randomized controlled trials in the general population to assess whether MTX can improve outcomes after myocardial infarction [33].

The only medications currently licensed for the treatment of dementia are acetylcholinesterase inhibitors and memantine. However, the effect of other drugs in dementia has been studied. Harmful results have been associated with aspirin use and statin use among women [34], although statins were initially reported as being protective in AD [9]. Protective effects of NSAIDs were reported in the 90s [9]. In addition, combined glucocorticoids and NSAID [35] or history of NSAID use in epidemiological studies [36] suggested decreased risk of dementia. Most recently, ibuprofen was associated with better cognitive performance in a large UK population cohort [37]. In our study, we controlled for NSAID use, and hence, the protective effect of cDMARDs observed is independent of NSAID use.

cDMARD therapy is effective at treating and controlling RA and hence may prove beneficial for the treatment of other inflammatory processes. AD, unambiguously a disorder with a considerable inflammatory component, might be one such disorder. However, although the contribution of inflammatory processes to the neuropathology of AD is considerable, suggesting a central nervous system target for antiinflammatory therapies, other evidence increasingly points to a peripheral inflammatory component to disease [38]. Furthermore, critically for potential therapeutic strategies, it is far from clear whether inflammation contributes to disease processes or is to some degree protective. Multiple observational studies are in line with the inflammation element of AD being disease exacerbating, not least as NSAIDs reduce the risk of AD in observational, real-world studies [39]. The findings presented here suggest a relatively robust protective effect of cDMARDs, especially MTX,

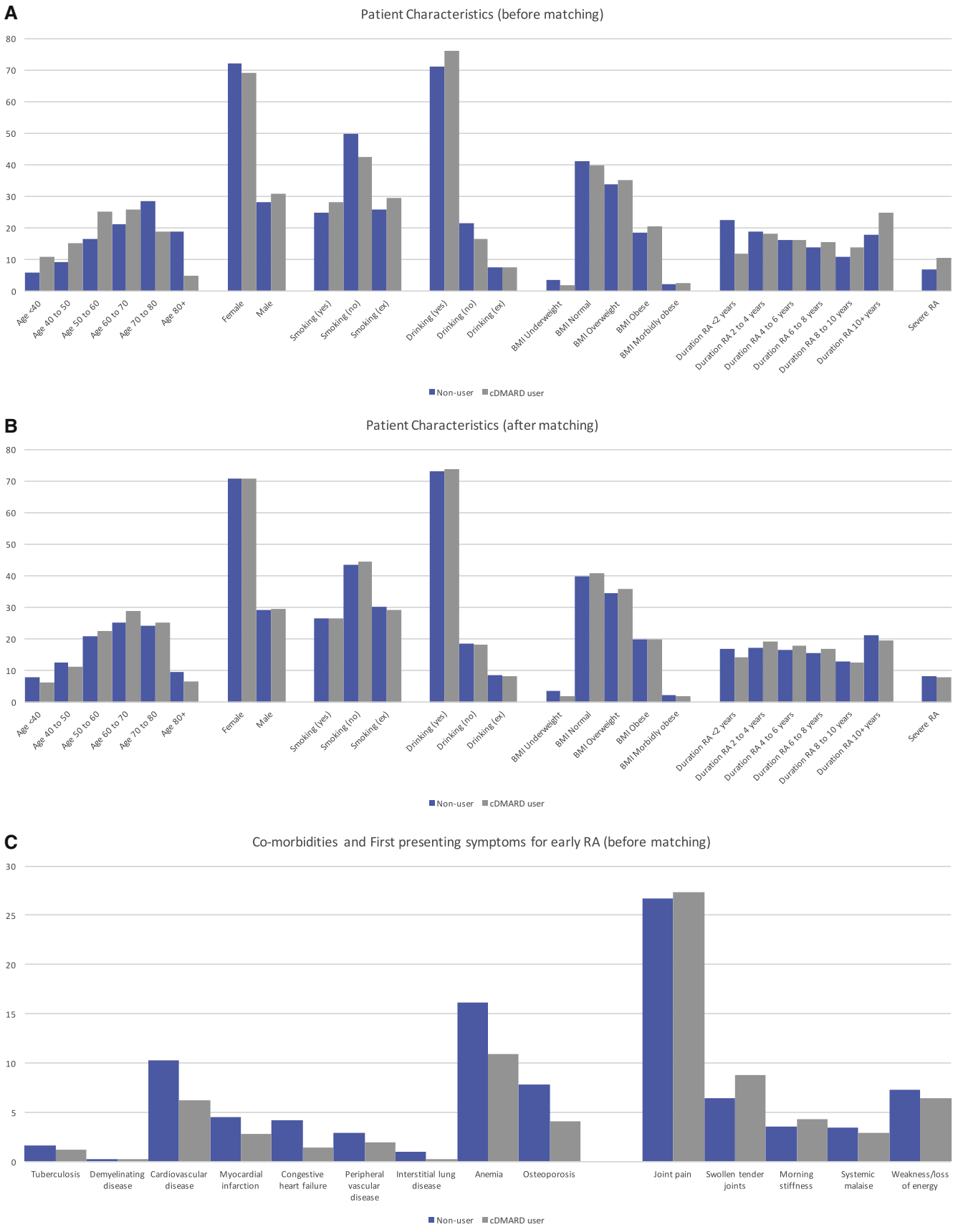
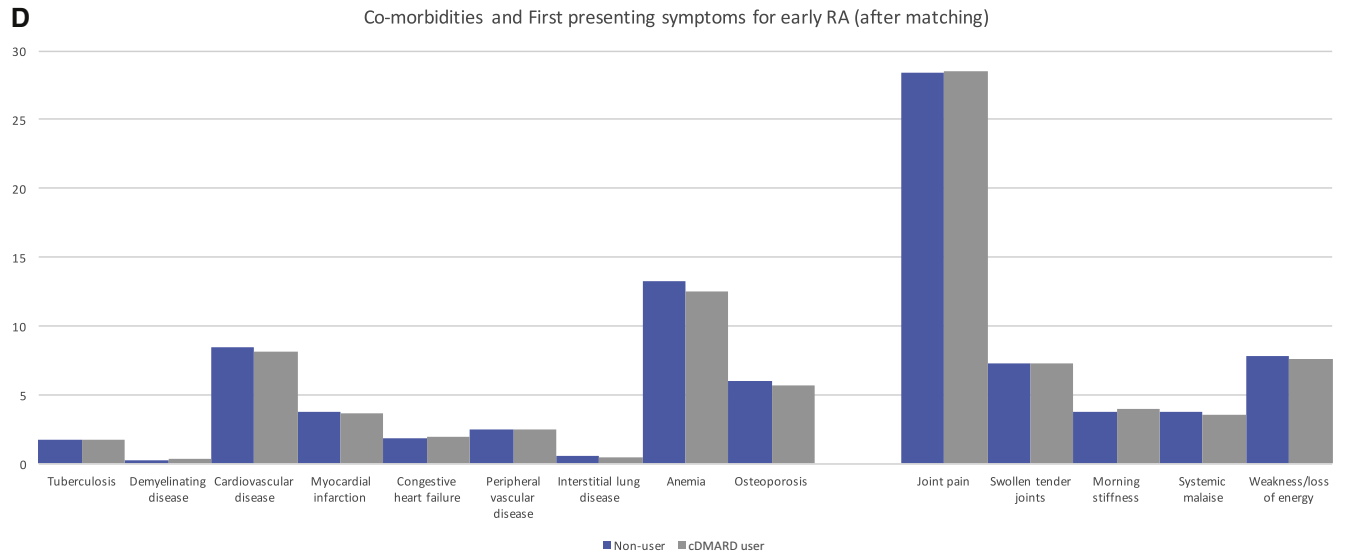
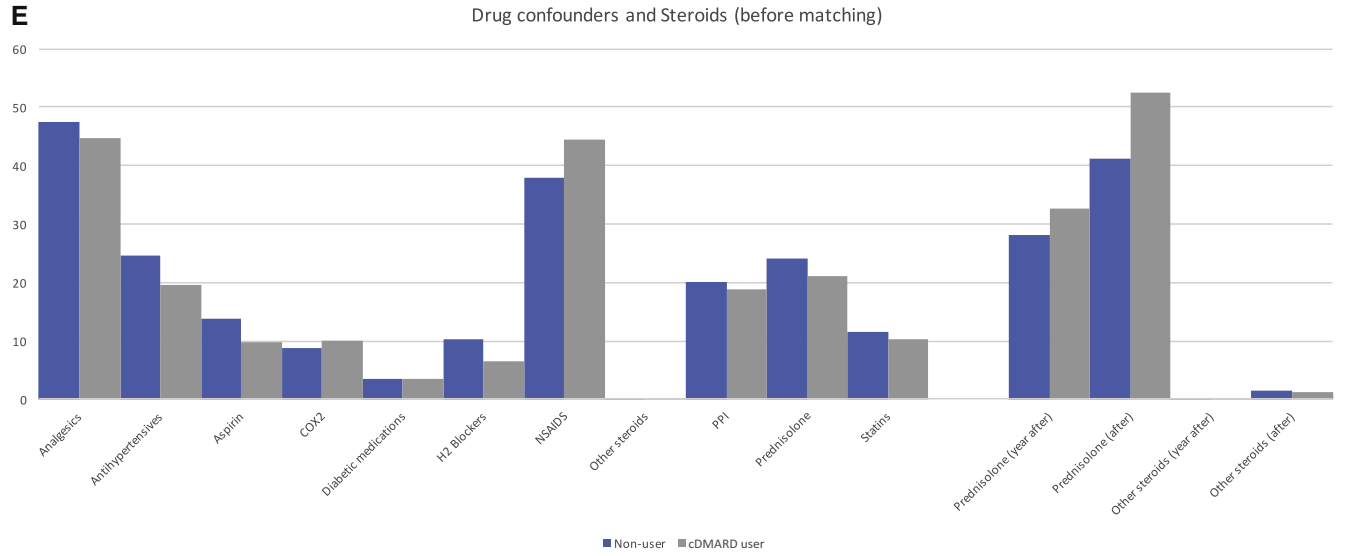


Fig. 1. Baseline characteristics of patients, both in the whole cohort and in the propensity-score-matched (1 to 2) data sets: cDMARD user versus nonuser. Abbreviations: BMI, body mass index; cDMARD, classical disease-modifying antirheumatic drugs; COX2, cyclooxygenase-2; NSAID, nonsteroidal antiinflammatory drug; PPI, proton pump inhibitors; RA, rheumatoid arthritis.





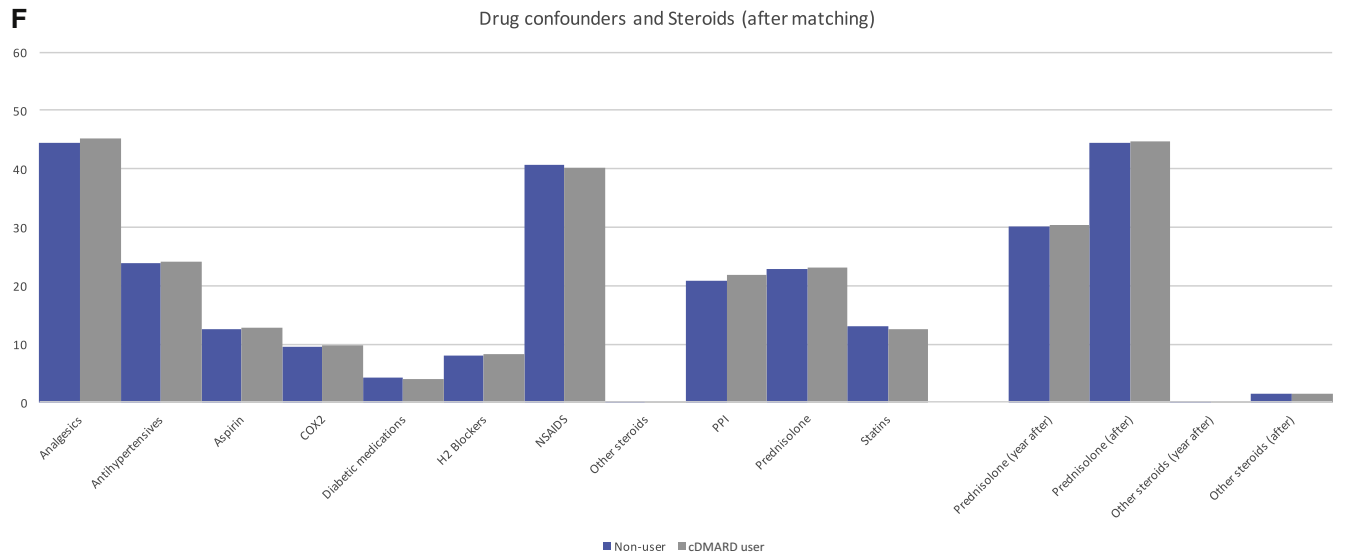


Fig. 1. (*Continued*)

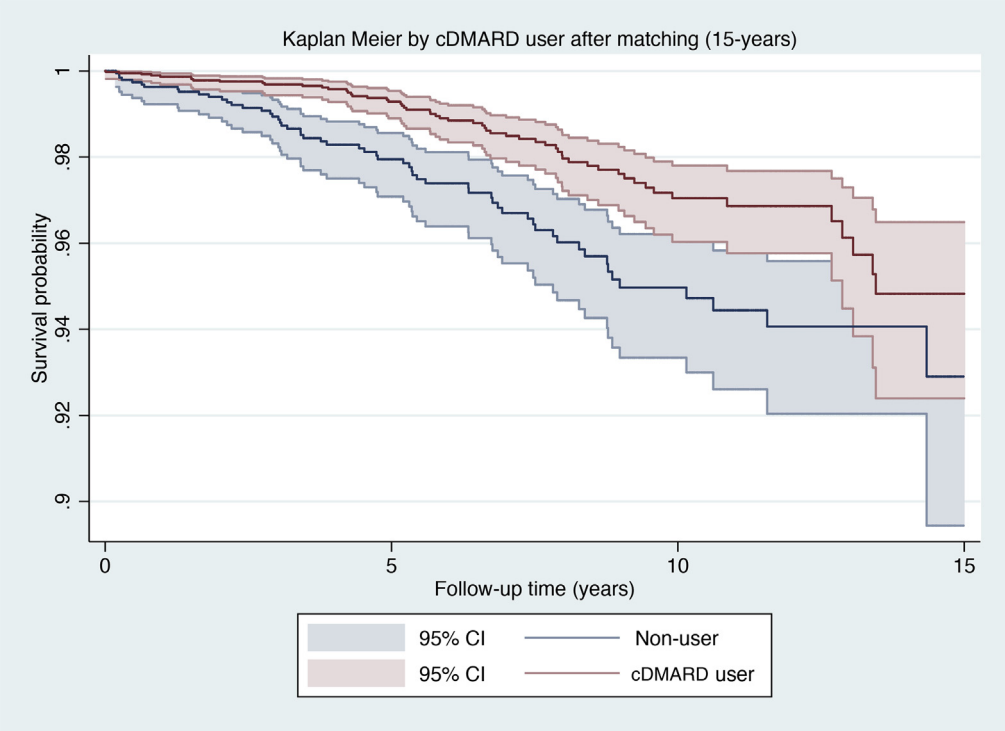


Fig. 2. Kaplan-Meier plot of the effect of cDMARD use on dementia. Abbreviations: cDMARD, classical disease-modifying antirheumatic drugs; CI, confidence interval.

independent of NSAIDs, adding considerably to the evidence that inflammation exacerbates disease and antiinflammatory agents might have value as disease-modifying agents. MTX, the cDMARD having the most effect, shows relatively little penetrance of the blood-brain barrier, but even a modest penetrance might have therapeutic benefit, as suggested by its use for some brain tumors that are treated with high doses of MTX [40]. Whether the lower dose as used in clinical practice for RA would be sufficient to cross the blood-brain barrier to have a central effect in AD protection, or whether the strong protection observed in this study suggests instead a peripheral action, raises a number of important questions for further study. These primarily include whether DMARDs cross the blood-brain barrier; whether DMARDs affect central nervous system inflammation; and evidence of central nervous system inflammation in RA. Although there is evidence suggesting the presence of central nervous system inflammation in dementia, particularly AD, there is a need for a valid and practical biomarker to assess the role of antiinflammatory treatments.

In summary, the significant reduction in dementia risk in cDMARD users observed in this study provides an important potential therapeutic option worthy of consideration in future randomized control trials.

4.3. Strengths and limitations

One of the strengths of this study is the UK CPRD data on which it is based with detailed date-stamped patient event data in primary and secondary care settings. The CPRD practice network covers all of the United Kingdom, and approximately 5% of all practices are covered by the CPRD. People included in CPRD are broadly representative of the UK population as a whole with respect to age, sex, socioeconomic status, and UK region [41,42]. The high degree of generalizability afforded by this very large sample enables population-level inferences to be made, and the longitudinal nature of the data allowed us to explore association of cDMARD use on dementia over a 15-year period of follow-up.

A possible limitation of the study is the lack of validation of individual cases of dementia in CPRD. Nevertheless, a systematic review found a high positive predictive value reporting diagnosis of dementia 83.2 (95% CI: 74.1–90.1) using CPRD [43]. Coding of the diagnosis of RA is also another potential limitation of the study. However, previous studies have shown the validity of an RA diagnosis in CPRD to be high [11]. A limitation is that it is not possible to study biologic drug usage within CPRD (biologics are given by injection or intravenously). Within this study, we only included incident patients, UK National Guidelines recommend cDMARDs as first-line therapy in early RA with progression to a biologic for patients with inadequate response, and a large proportion of patients do not need biologic therapy in the first 2 years of disease [44]. The publication of the National Institute for Health and Care Excellence technology appraisal 36, in March 2002, provided guidance on the use of etanercept and infliximab as recommended treatment

options for those with severe RA failing to respond to the two cDMARDs. It is possible that some of the patients in our data set with severe RA are biologic users. However, at the time of this CPRD datacut, only a minority of patients with RA would have been receiving biological agents, and 60%–70% of these would have been taking MTX as well as the biological agent. We tested for evidence of an interaction between year of RA diagnosis (pre-and post-2002 before and after the introduction of biologics came into widespread use) and cDMARD use on dementia outcome, and the interaction was not significant ($P = .47$); hence, biologic use is unlikely to influence our findings.

Similar to others, we have used an intention-to-treat definition of cDMARD exposure, irrespective of adherence to therapy [45]. To overcome the effect of confounding by indication, we used propensity score matching on known measurable confounders, a strength of the study being the comprehensive and detailed information on patient characteristics, medication use, and comorbidities, particularly in respect of traditional and disease-specific risk factors for cardiovascular disease. Adjustment for length of follow-up and year of RA diagnosis allowed us to control for changing trends in both dementia and cDMARD use over time, in addition to equalizing potential follow-up time in the exposure groups. Furthermore, our modeling of mortality as a competing event in analyses of time to dementia addressed the issue of mortality precluding the experience of such events, which otherwise would likely bias estimates of risk.

The results of the study are for the matched population, which is a strength of the study as it minimizes bias due to confounding by indication but limits the generalizability of the findings. In addition, owing to the observational nature of the study, there remains the potential for residual confounding that could attenuate or explain the observed associations, due to unmeasured variables such as arthritis disease severity, health, and lifestyle effects.

4.4. What does this study add?

This study is the first to demonstrate a strong beneficial effect of cDMARDs by suggesting a halving of risk of dementia. This finding requires replication in other large observation studies and may provide an important therapeutic pharmacological treatment for dementia to test in a future randomized controlled trial.

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Ethical approval: The CPRD Group has obtained ethical approval from a National Research Ethics Service (NRES) committee for all purely observational research using anonymized CPRD data; namely, studies which do not include patient involvement. The study has been approved by ISAC (Independent Scientific Advisory Committee) for MHRA database research (protocol number 12_055R2).

Role of the funding source: The study sponsors had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2017.10.002.

RESEARCH IN CONTEXT

1. Systematic review: The definition and context for rheumatoid arthritis and dementia was searched in the UK National Institute for Health and Care Excellence guidelines. Literature was reviewed from PubMed and the catalog of libraries of the University of Oxford for meeting abstracts and presentations. We hypothesized a potential impact of classical disease-modifying antirheumatic drug (cDMARD) use on dementia development in patients with rheumatoid arthritis because cDMARDs are widely used to control this inflammatory disease and it is accepted that dementia is an inflammatory disease too.
2. Interpretation: To support this potential effect, we present a case definition for RA, dementia, and cDMARDs together with robust analyses at a national level. Our findings demonstrate a strong beneficial effect of cDMARD use on dementia.
3. Future directions: It will require further studies in randomized clinical trials to validate cDMARDs as a therapeutic pharmacological treatment for dementia.

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